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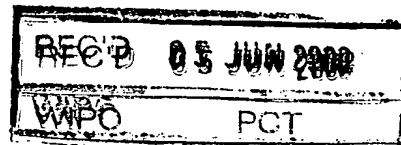
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EP 00/03747

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Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

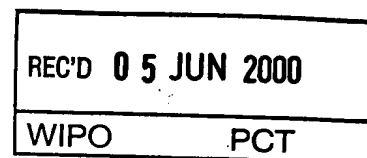
The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

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Patentanmeldung Nr. Patent application No. Demande de brevet n°

99201390.4



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**Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation**

Anmeldung Nr.:
Application no.:
Demande n°: 99201390.4

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Date of filing: 29/04/99
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
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NETHERLANDS

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:

Use of Org 33245 for contraception, hormone replacement therapy and minimizing uterine bleeding

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

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A61K31/58

Am Anmeldetag benannte Vertragsstaaten:
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Remarques:

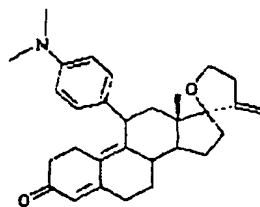
The original title of the application reads as follows:
Use of antiprogestagens in combined therapy.

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USE OF ANTIPROGESTAGENS IN COMBINED THERAPY

The invention pertains to an anti-progestagenic steroid of the 11β -aryl, 17-spiromethylene type. Such antiprogestational compounds are known from EP 549041 and EP 582338. As described, their therapeutic use is associated with several advantages, int.al. in view of a strong activity and high selectivity, in which these compounds are markedly distinct from RU 486, which holds as the reference anti-progestagen in the field.

It has now been found that within this known group of 11β -aryl, 17-spiromethylene steroids, one of these compounds has a surprisingly better suitability than the others for being administered intermittently. This is the compound satisfying the structural formula I given below, hereinafter referred to as Org 33245:



Formula I

This particular compound therewith has the highly advantageous property that it can be used in the specific medical application of combined therapy with progestagen-only preparations.

Progestagen-only preparations for contraception or HRT (hormone replacement therapy) are known. Contraceptive regimens of this type are usually referred to as "progestagen-only pill" or "POP". Such POPs have the general advantage of avoiding the administration of estrogens. It is known to use anti-progestagens in order to improve the effects of the administration of progestagen-only preparations. This particularly relates to an improved bleeding pattern. Thus major improvements have been proposed, according to which the anti-progestagen is administered periodically,

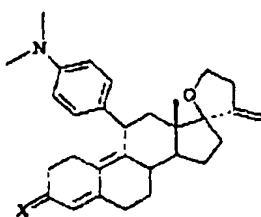
which leads to bleeding patterns that more closely resemble the natural menstrual cycle. One such improvement is that according to Hodgen, see WO 93/21927, wherein a contraceptive regimen free from estrogens is described, in which the active, ovulation-inhibiting ingredient is a progestational agent, and wherein an anti-progestagen is administered intermittently in order to achieve better bleeding (int.al. minimizing progestagen-associated breakthrough bleeding). The anti-progestagen is administered e.g. once every 30, 60, 90, or 120 days, and preferably once every cycle of 30 days (most preferably on day 28 of each cycle). Another such improvement is that according to WO 97/49407, in which it is described to administer, in addition to a progestagen-only preparation, two to seven dosage units comprising an anti-progestagen, one of which is administered at the beginning of a cycle, the other or others divided regularly throughout the cycle (which is described as being 20-32 days and preferably 28).

It has been found that, surprisingly, Org 33245 not only has a strong activity and high selectivity, but also shows a strong binding to human orosomucoid, which is indicative of a relatively long half life (Steingold et al. 1990, American Journal of Obstetrics and Gynaecology 162, 532-524). This makes the compound extremely well suitable for intermittent administration, and much better so than anti-progestagens proposed earlier for this use, such as RU 486 and Org 33628.

It should be noted that the excellent suitability of Org 33245 comes all the more as a surprise since this could not be expected from the closely related progestagen Org 33628 which, in fact, has been proposed for use in the regimens described in EP 549041 and EP 582338. Org 33628, although being highly advantageous from the perspective of cost-price and activity, suffers from a drawback particularly associated with intermittent use. This drawback is its relatively rapid metabolism, as can be seen from the short half-life in humans (about 12 hours). This confronts the person skilled in the art with the problem of finding an alternative which has the advantages of Org 33628, but does not have this drawback.

The invention obviates this drawback by providing the use of Org 33245 in the manufacture of a preparation for the intermittent administration in the course of progestagen-only therapy (including contraception). Put otherwise, the invention is a method of treatment involving progestagen-only therapy in combination with the intermittent administration of Org 33245. The invention also pertains to a combination comprising a progestagen and an anti-progestagen, wherein the anti-progestagen is Org 33245.

- As will be easily understood by the person skilled in the art, it is intended to include in the invention the compound of formula I, as well as prodrugs and precursors thereof, i.e. those closely related compounds the substituents of which are easily metabolised to the active compound according to formula I, or are readily cleaved to such a compound upon being administered. Together with the most regular prodrugs, the invention thus pertains to the compounds satisfying formula II, and pharmaceutically acceptable salts thereof.



Formula II

- wherein X stands for (H,H), (O), or (N-OH); The 3-keto compound, i.e. Org 33245 itself in which X is (O), is preferred. The other possibilities for the substituent at carbon atom number 3 have as their main property according to the invention that they are precursors (prodrugs) of the preferred 3-keto compound. For the sake of clarity, the invention is described hereinafter with reference to Org 33245 itself.

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For the preparation of Org 33245 reference is made to EP 549041 and EP 582338, more specifically Example 1 of EP 549041. In the intermittent use according to the

invention, Org 33245 will generally be employed in a dosage amount ranging from 0.1 to 300 mg, and preferably 0.5 to 150 mg. The dosage amount of Org 33245 can be the same each time it is administered, but it may also be used in decreasing amounts as described in WO 97/49407.

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The type of administration of Org 33245 can be any type which is suitable for intermittent administration, i.e. it could include an injection which can be given once or several times a month, or it could include a transdermal patch which is applied and removed again once or several times a month, in each case leaving the majority of
10 days without the administration of Org 33245. However, the most convenient and desired form for the intermittent administration of Org 33245 is by way of an oral dosage unit, preferably a tablet.

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The intermittent administration of Org 33245 is particularly advantageous in the course of progestagen-only therapy (including contraception). While the anti-progestagen is given intermittently, i.e. on certain days only, it is preferred that on such a day, it is administered together with the progestagen dosage. While an anti-progestagen with a too rapid metabolism will require a precise point in time of administration, and not necessarily simultaneously with the progestagen, Org 33245
20 can be given in a form physically combined with the progestagen. Thus the invention also includes a combined dosage unit comprising a progestagen and an anti-progestagen, wherein the anti-progestagen is Org 33245.

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The invention includes a drug delivery system for contraceptive use (a contraceptive kit) containing daily oral dosage units, each unit containing a progestagen, and 1-7, preferably 1-4 units comprising an anti-progestagen, preferably combined with the progestagen. One of the anti-progestagen dosage units is administered at the end (or, for that matter, the beginning) of a cycle. In fact the anti-progestagen dosage which is given once a cycle, marks the transition from one cycle to the next (i.e. the term "end
30 of the cycle" can be interpreted as the "beginning" of a cycle as well). A second anti-

progestagen dosage unit, if given, is administered in the middle of the cycle. If more than two anti-progestagen dosage units are employed, one is given at the end of a cycle, the others orderly divided through the cycle. The preferred dosage regimens are those specifically described in WO 93/21927 and WO 97/49407. The term "cycle" refers to a period of generally 20-35 days, and preferably more close to the natural menstrual cycle, i.e. 28-32 days.

The invention also includes a drug delivery system for HRT (hormone replacement therapy) containing daily oral dosage units, each unit comprising a progestagen with or without an estrogen or an estrogen only, and 1-7, preferably 1-4 dosage units comprising an anti-progestagen, one of which is preferably administered at the beginning of a cycle and the others orderly divided through the cycle (if one other: in the middle of the cycle).

In general terms the invention relates to a contraceptive and/or HRT (hormone replacement therapy) kit comprising sequential daily dosage units for oral administration each comprising as the sole contraceptively effective ingredient a progestagen, or as effective ingredient for HRT a progestagen with or without an estrogen or an estrogen alone, and further two or more units comprising an anti-progestagen.

If desired the kits may contain placebo pills to bridge two periods of administration of active ingredients.

The invention also includes a pharmaceutical product (i.e. the dosage units or the package containing the dosage units), a method of using the product, and a process of manufacturing the pharmaceutical product.

The invention also includes a method of providing contraception and/or HRT for a pre-, peri-, or post-menopausal woman involving administering to the woman the

above-mentioned regimens. Thus, the invention also resides in a method of contraception comprising daily administering to a female of child-bearing age a contraceptively effective amount of a progestagen and intermittently administering an anti-progestagen, wherein the anti-progestagen is Org 33245. In another aspect, the invention resides in a method of treatment of irregular or breakthrough bleeding in a female using a progestagen-only preparation, comprising intermittently administering Org 33245. In these methods it is preferred if Org 33245 is administered on 1-4 days in a cycle of 28-32 days, divided over said cycle, with one of the administrations usually considered the end (or, for that matter, the beginning) of a cycle.

Progestagens for use with the invention are 3-keto-desogestrel (etonogestrel), desogestrel, gestodene, levonorgestrel, norgestrel and other progestagens commonly used for contraception and HRT. Desogestrel has the chemical name 13-ethyl-11-methylene-18,19-di-nor-17 α -pregn-4-en-20-yn-17-ol, and is the preferred progestagen. Desogestrel is believed to be metabolized in the body into 3-ketodesogestrel. Preferably, the dosage units contain 75 μ g of desogestrel or 3-ketodesogestrel, or an amount of other progestagens having the equivalent effect of 75 μ g of desogestrel. Based on practically applied doses, levonorgestrel, desogestrel, and 3-keto-desogestrel are relatively equipotent in progestagenic activity. Gestodene is approximately 1.5 times as potent as these compounds. Norgestrel is about half as potent as levonorgestrel. A further preferred progestagen is Org 30659, see int. al. EP 897927.

The invention will be explained further with reference to the following examples.

Example 1

Org 33245 ((11 β ,17 α)-17,23-epoxy-11-[(4-dimethylamino)phenyl]-19,24-dinorchola-4,9,20-trien-3-one) is synthesized according to Example 1 of EP 549041.

Example 2

A pharmaceutical composition is prepared containing a steroid in accordance with the present invention. Org 33245 is mixed with the other ingredients in a standard way, and the mixture is subjected to granulation. The composition is as follows:

Org 33245 (active)	1-10 wt.%;
Corn Starch (disintegrant)	15 wt.%;
Hydroxy Propyl Cellulose (binder)	3 wt.%;
Lactose 200 M (diluent) up to	100 wt.%;

The resulting granules can be used for tableting following procedures regularly available in the art, so as to make a dosage unit suitable for use in the invention.

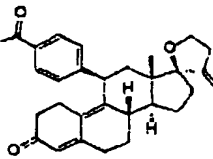
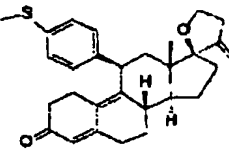
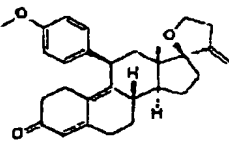
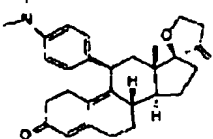
15 Example 3

The binding to orosomucoid is determined as described in Philibert et al., Antihormones in Health and Disease (M.K. Agarwal, ed.), 1991, 19, 1-17. The results are depicted in the Table below. The results show that, while the binding of the other anti-progestagens tested is lower than that of RU 486 (100%), Org 33245 constitutes a marked improvement.

Example 4

Anti-progestagenic activity is determined by using an anti-McPhail test as known to the person skilled in the art and described, int.al., in Kloosterboer et al., Human Reproduction (1994), Volume 9, Supplement 1, pages 47-52. Results in terms of the Minimum Active Dose (MAD) are given in the Table below.

TABLE

Compound	Binding affinity to orosomucoid (relative to RU 486)	Anti-McPhail Assay (MAD)
	13,5 %	8 mg/kg
	82 %	> 1 mg/kg
	64 %	1 mg/kg
	222 %	0.5 mg/kg

Claims:

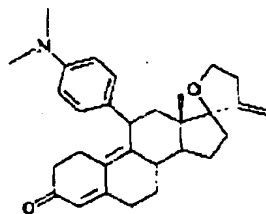
1. The use of Org 33245 as defined in the description for the manufacture of a contraceptive or HRT agent wherein Org 33245 is to be administered
5 intermittently.
2. A use according to claim 1, characterised in that the intermittent administration of Org 33245 takes place as an addition to progestagen-only therapy.
- 10 3. The use of Org 33245 for the manufacture of a medicament for minimizing uterine bleeding in a female using a progestin-only pharmaceutical preparation, characterized in that the anti-progestagen is Org 33245 as defined in the description.
- 15 4. A use according to any of the preceding claims, characterised in that a dosage of Org 33245 is to be administered 1-7 days during a cycle of 28-32 days, wherein one dosage marks the end of a cycle and the optional other dosages are to be administered regularly divided over the remaining days of the cycle.
- 20 5. A contraceptive kit providing means (a) for the daily administration of a progestagen and means (b) for the intermittent administration of an anti-progestagen, wherein the latter means (b) comprises as the anti-progestagen the compound Org 33245 as defined in the description.
- 25 6. A combined means for the dosage of a progestagen and an anti-progestagen, characterised in that the anti-progestagen is Org 33245 as defined in the description.
- 30 7. A method of contraception comprising daily administering to a female of child-bearing age a contraceptively effective amount of a progestagen and intermittently

administering an anti-progestagen, wherein the anti-progestagen is Org 33245 as defined in the description.

- 5 8. A method of treatment of irregular or breakthrough uterine bleeding in a female using a progestagen-only preparation, comprising intermittently administering an anti-progestagen, wherein the anti-progestagen is Org 33245 as defined in the description.
- 10 9. A method according to claim 7 or 8, wherein the anti-progestagen is administered on 1-4 days in a cycle of 28-32 days.

ABSTRACT

It has been found that the compound satisfying the structural formula I given below has a surprisingly good suitability for being administered intermittently:

**Formula I**

This particular compound therewith has the highly advantageous property that it can be used in the specific medical application of combined therapy with progestagen-only preparations.

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